L5: Entry 7 of 72 File: USPT May 27, 2003

US-PAT-NO: 6569688
DOCUMENT-IDENTIFIER: US 6569688 B2

TITLE: Intravascular apparatus method

DATE-ISSUED: May 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 09/ 486362 [PALM]
DATE FILED: February 28, 2000

PARENT-CASE:
This application is a 371 of PCT/US98/16823 which is a divisional of Ser. No. 08/917,609 filed Aug. 26, 1997, now abandoned.

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/US98/16823	August 13, 1998	WO99/09912	Mar 4, 1999		

INT-CL: [07] G01 N 33/543

US-CL-ISSUED: 436/518; 435/4, 435/287.9, 424/1.29, 424/9.33, 422/57, 436/524
US-CL-CURRENT: 436/518; 422/57, 424/1.29, 424/9.33, 435/287.9, 435/4, 436/524

FIELD-OF-SEARCH: 422/57, 422/294, 536/24.5, 435/174, 435/4, 435/176, 435/7.1, 435/180, 435/182, 435/188.5, 424/146.1, 424/94.1, 424/1.29, 424/9.322, 424/410, 558/299, 623/1, 623/1.12, 606/194, 606/195, 436/518, 436/524

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5314688	May 1994	Kauffman et al.	
☐	5428070	June 1995	Cooke et al.	514/557
☐	5429634	July 1995	Narciso, Jr.	
☐	5441515	August 1995	Khosravi et al.	606/194
☐	5500013	March 1996	Buscemi et al.	
☐	5512291	April 1996	Li	
☐	5514379	May 1996	Weissleder et al.	
☐	5578075	November 1996	Dayton et al.	424/422
☐	5833651	November 1998	Donovan et al.	604/509
☐	5925353	July 1999	Mosseri et al.	424/178.1
☐	6143037	November 2000	Goldstein et al.	623/1.15
☐	6180824	January 2001	Stamler et al.	562/507

ART-UNIT: 1641

PRIMARY-EXAMINER: Le; Long V.

ASSISTANT-EXAMINER: Counts; Gary

ATTY-AGENT-FIRM: G. E. Ehrlich Ltd.

ABSTRACT:

Intravascular apparatus and method for locally treating a patient's blood vessel, are provided. The apparatus includes an implanted carrier (2) for insertion into the vessel; and a biologically active agent (8) immobilized to the carrier (2), said biologically active agent (8) reacting with a first substance to produce a second substance. The second substance is preferably a therapeutic agent, such as nitric oxide, for locally treating the vessel. The biologically active agent (8) is preferably an enzyme such as nitrogen oxide synthase, and the first substance is preferably arginine introduced to the patient's body as part of a diet. According to another embodiment, the biologically active agent (8) is a catalytic antibody and the first substance is a prodrug. Alternatively, the biologically active agent (8) is a ribozyme. The method includes introducing into a patient's vessel an implantable carrier including a biologically active agent immobilized thereto, and reacting the biologically active agent with a first substance to locally produce a second substance.

31 Claims, 1 Drawing figures

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L5: Entry 60 of 72 File: USPT Jun 2, 1998

DOCUMENT-IDENTIFIER: US 5759836 A
TITLE: Osteoarthritis-associated inducable isoform of nitric oxide synthetase

Detailed Description Text (24):
After the introduction of the vector, the host cells are grown in a selective medium, which selects for the growth of vector-containing cells. Expression of the cloned gene sequence(s) results in the production of the OA-NOS. The expressed protein is then isolated and purified by any conventional procedure involving extraction, precipitation, chromatography, electrophoresis, or the like, or by affinity chromatography, using ncNOC or anti-OA-NOS monoclonal antibodies immobilized on a gel matrix contained within a column. Crude preparations containing the recombinant OA-NOS are passed through the column whereby the OA-NOS will be bound to the column by the specific antibody while the impurities will pass through. After washing, the protein is eluted from the gel at a high pH, e.g., pH 11.

Detailed Description Text (44):
The biological sample may be treated with a solid phase support or carrier (which terms are used interchangeably herein) such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled OA-NOS-specific antibody. The solid phase support may then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on said solid support may then be detected by conventional means.

Detailed Description Text (58):
Antibodies or other molecules which include the antigen-binding portion of an antibody may also be used for isolation and purification of OA-NOS. Thus, for example, antibodies specific to OA-NOS can be immobilized on a solid phase support or carrier with which an impure solution containing OA-NOS is brought into contact. The OA-NOS will bind to the antibodies which are in turn bound to the support while all of the contaminants are washed away. Pure OA-NOS can then be eluted from the support by means well-known in the art.

Detailed Description Text (120):
Partial amino acid sequencing of human OA-NOS. The purified OA-NOS will be sequenced to verify its identity and will also be used to design primers to clone the cDNA by RT-PCR. The purified OA-NOS will be subject to immobilized V-8 protease cleavage and run on an 5-20%, gradient SDS-PAGE gel (Cleveland et al., 1977). The peptide will be transferred to a PVDF (polyvinylidene difluoride) membrane as described by Matsudaira (J. Biol. Chem. 262:10035-10038, 1987) and amino acid sequenced.

Other Reference Publication (15):
Stefanovic-Racic et al, N-Monomethyl Arginine, an Inhibitor of Nitric Oxide Synthase, Suppresses the Development of Adjuvant Arthritis in Rats, Arthritis & Rhfeumatism vol. 37, No. 7, pp. 1062-1069, Jul. 1994.

WEST Search History

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DATE: Monday, October 25, 2004

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☐	L5	l4 and immobiliz$	72
☐	L4	arginine adj5 (nitric adj1 oxide)	526
☐	L3	argine adj5 (nitric adj1 oxide)	1
☐	L2	argine adj5 no	0
☐	L1	urokinase adj5 arginine	67

END OF SEARCH HISTORY

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L1: Entry 2 of 67 File: USPT Aug 24, 2004

DOCUMENT-IDENTIFIER: US 6780849 B2
TITLE: Lipid-based nitric oxide donors

Detailed Description Text (58):
Exemplary non-genetic therapeutic agents include: anti-thrombotic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone); anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine and mesalamine; antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, angiopeptin, monoclonal antibodies capable of blocking smooth muscle cell proliferation, and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, hirudin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides; vascular cell growth promoters such as growth factors, including platelet-derived growth factor, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; protein kinase and tyrosine kinase inhibitors (e.g., tyrphostins, genistein, quinoxalines); prostacyclin analogs; cholesterol-lowering agents; angiopoietins; antimicrobial agents such as triclosan, cephalosporins, aminoglycosides and nitrofurantoin; cytotoxic agents, cytostatic agents and cell proliferation affectors; vasodilating agents; and agents that interfere with endogenous vascoactive mechanisms.

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L1: Entry 4 of 67 File: USPT Jun 22, 2004

DOCUMENT-IDENTIFIER: US 6752829 B2
TITLE: Stent with channel(s) for containing and delivering a biologically active material and method for manufacturing the same

Detailed Description Text (23):
anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone);

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L1: Entry 54 of 67 File: USPT Feb 13, 1996

DOCUMENT-IDENTIFIER: US 5490981 A
TITLE: Diagnostic and therapeutic compositions and methods for lipoprotein(a)

Brief Summary Text (6):
The structure of the lipoprotein(a) molecule has been determined to comprise a protein portion identified as apolipoprotein B-100 linked through disulfide bonds to two apolipoprotein(a) molecules. The structure of lipoprotein(a) is similar to that of plasminogen, a blood component involved in vessel wound repair which is activated by proteolytic cleavage at a specific activation site by tissue-type plasminogen activator (t-PA) or urokinase. The region encompassing the plasminogen activation site ("activation site region") differs in amino acid sequence the analogous apolipoprotein(a) region. The sequence around the plasminogen activation site (arginine-valine) is (SEQ ID NO:5) LYS-CYS-PRO-GLY-ARG-VAL-VAL-GLY-GLY, whereas the analogous apolipoprotein(a) sequence is (SEQ ID NO:6) LYS-CYS-PRO-GLY-SER-ILE-VAL-GLY-GLY. See Eaton et al., Proc. Natl. Acad. Sci. USA, 84: 3224-3228, 3227 (1987), the disclosure of which is incorporated herein. Moreover, while plasminogen is activated by cleavage by urokinase or t-PA at arginine 560, apolipoprotein(a) may be inactive or not activatable by streptokinase, urokinase or t-PA. Id. For purposes of this disclosure, the above-described region of apolipoprotein(a) that is analogous to the activation site region of plasminogen will be hereinafter referred to as "the activation site region of apolipoprotein (a)."

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L1: Entry 57 of 67 File: USPT Aug 16, 1988

DOCUMENT-IDENTIFIER: US 4764466 A
TITLE: Method for stabilizing an immobilized fibrinolytic enzyme

Detailed Description Text (36):
The procedures of Example 1 were repeated except that histidine was replaced by arginine. The activity of urokinase immobilized on the arginine-treated film was 576 mm.sup.2 : the film formed a circular plaque (24 mm.phi.) by lysing the fibrin. As a control, urokinase was immobilized on an arginine-untreated film and its fibrinolytic activity was also 576 mm.sup.2.

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L5: Entry 5 of 72 File: USPT Mar 16, 2004

DOCUMENT-IDENTIFIER: US 6706274 B2
** See image for Certificate of Correction **
TITLE: Differential delivery of nitric oxide

Detailed Description Text (22):
For example, in some instances it is desirable to select a matrix configuration that will control the release of the nitric oxide donor compound itself. As a specific example, a donor compound may be selected that does not substantially release/produce nitric oxide until contact is made with tissue outside of the matrix (a specific example is L-arginine, which acts as an enzyme substrate for the formation of nitric oxide within vascular tissue, such as the endothelium). In such instances, the matrix configuration is typically designed to release the nitric oxide donor compound, for example, by transporting it from the matrix or by releasing it from the matrix due to matrix degradation.

Detailed Description Text (40):
The nitric oxide donor compounds having differing half-lives can also be introduced to the body (1) by adsorbing or immobilizing them on the surface of a medical article or (2) by placing them in a solution or dispersion which is subsequently exposed to a local site of interest via a medical article (for example, by use of an infusion catheter or endoluminal paving device) or is injected into the tissue from a medical article (for example, by use of an injection catheter).

Detailed Description Text (59):
In addition to being placed in matrix configurations, the compounds having differing nitric oxide release mechanisms can also be: (1) adsorbed or immobilized on the surface of a medical article, or (2) placed in a solution or dispersion which is subsequently exposed to a local site of interest (for example, by use of infusion catheters) or is injected into tissue (for example, by use of an injection catheter).

L5: Entry 27 of 72 File: USPT Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6210918 B1
TITLE: Non-invasive method for detection, diagnosis or prediction of term or pre-term labor

Brief Summary Text (12):
Nitric oxide (NO) is a free radical with a very short half-life. Nitric oxide is synthesized from the amino acid L-arginine by the nitric oxide synthase (NOS). So far, the only clearly established role for nitric oxide is as a cytotoxic molecule for invading microorganisms and tumor cells. However, other physiological activity, such as acting as a neurotransmitter in the brain and in the periphery, affecting gastrointestinal tract motility and penile erection were also observed. Nitric oxide is produced in vascular endothelial cells by the nitric oxide synthase and seems to mediate vascular smooth muscle relaxation by increasing levels of cGMP. Its effect on relaxation of intrapulmonary artery and vein was described in J. Pharmacol. Exp. Ther., 228:33-42 (1984).

Detailed Description Text (16):
Nitric oxide synthase (iNOS) is the enzyme which converts nitric oxide substrate (L-arginine) to nitric oxide and citrulline. Consequently, such conversion of arginine to citrulline and the quantitation of such reaction is one of the methods used for detection of level of nitric oxide. Other methods involve enzymatic assays, measurement of levels of nitrate, nitrite, citrulline, NO, electron paramagnetic resonance, or immunological assays, immunohistochemistry, fluorescence for nitrate, etc.

Detailed Description Text (91):
Effect of substrate for nitric oxide synthase, on preterm labor inhibition was also studied. Neither the administration of the substrate, L-arginine, to the contracting uterus, nor infusion of nitric oxide synthase inhibitors into the quiescent uterus were able to change the uterine contractility index. This suggested that nitric oxide availability in the intact pregnant monkey was not substrate dependent and sensitive. However, these compounds were observed to have an effect in human patients and in other species.

Detailed Description Text (108):
Consequently, currently the most preferred methods for detection of NO are indirect assays such as measurements of cGMP which determines the effect of nitric oxide on granulate cyclase, measurement of nitrite accumulation which determines NO oxidation, measurement of citrulline, a coproduct of nitric oxide synthase, measurement of L-arginine, nitric oxide precursor, or measurement of iNOS, the enzyme which converts arginine to NO and citrulline.

Detailed Description Text (109):
Diagnostic methods of the invention are therefore directed to detection of nitric oxide, to the enzyme producing nitric oxide, nitric oxide synthase, nitric oxide precursor arginine and citrulline, which is a nitric oxide coproduct of the reaction producing nitric oxide from arginine, or detection of nitrate or nitrite as markers for nitric oxide or nitric oxide synthase.

Detailed Description Text (124):

Kits for detection of NO, NO.sub.2 /NO.sub.3, arginine, citrulline or iNOS may contain, for example, dip-stick containing a solid phase immobilized reagent for immunological or chromogenic detection of, for example, arginine, citrulline or nitrate/nitrite. Similarly, a reagent paper strip may contain immobilized enzymes such as urea cycle enzymes for conversion of arginine to citrulline.

Detailed Description Text (125):
Typically, there would be a solid phase having immobilized the reaction reagent, and liquid phase where the bodily fluid is brought into contact with the reagent.

Detailed Description Text (126):
For example, the kit would include the solid phase with immobilized specific iNOS antibody which would react with iNOS when iNOS is present in the sample.

Detailed Description Text (235):
Human patient has venous catheter introduced and a solution containing .sup.15 N arginine (5-100 mg) in saline, and of 0.4 ml of the [MGD).sub.2 /FE] complex (326 mg/kg of MGD and 34 mg/kg of FeSO.sub.4) is injected. Immediately after injection, the patient is transferred to the S-band EPR spectrometer and the arm with catheter is immobilized by taping down with a thin and narrow plexiglass plate and then placed inside the resonator. The in vivo EPR signal is recorded at 1 or 2 hours after the injection of the [(MGD).sub.2 /Fe] complex. The concentrations of the [(MGD).sub.2 /Fe--NO] complex in the urine samples are calculated by comparing the signal intensities obtained from the samples to the signal intensity of a standard solution containing 0.1 mM of the [(MGD).sub.2 /Fe--NO] complex.

Other Reference Publication (12):
P. M. Rhodes, et al., The L-Arginine:Nitric Oxide Pathway is the Major Source of Plasma Nitrite in Fasted Humans, Biochemical and Biophysical Research Communications, 209/2, 590-596, (1995).

CLAIMS:

1. A non-invasive non-surgical method for detection, diagnosis or prediction of term or pre-term labor in a pregnant female, said method comprising steps:

(a) obtaining a sample of blood, plasma, serum, urine or saliva from the pregnant female;

(b) subjecting said sample to a procedure detecting a level of nitric oxide, arginine or citrulline, or activity of nitric oxide synthase, expression of nitric oxide synthase or conversion of nitric oxide to its metabolites nitrate and nitrite in said blood, plasma, serum, urine, saliva or a tissue sample obtained from the pregnant female;

(c) detecting, diagnosing or predicting said term or preterm labor by comparing levels of nitric oxide, arginine or citrulline, or activity of nitric oxide synthase, expression of nitric oxide synthase or conversion of nitric oxide to its metabolites nitrate and nitrite obtained from a tested female to levels obtained from a pregnant non-laboring female.

2. The method of claim 1 wherein the term or pre-term labor is detected, diagnosed or predicted by determination of decreased levels of nitric oxide, decreased conversion of arginine to citrulline, decreased conversion of nitric oxide to nitrate and nitrite markers and by detection of lower levels of nitrate and nitrite markers in plasma, serum or urine when compared to such levels obtained from the pregnant non-laboring female.

6. The method of claim 5 wherein the citrulline is detected by high pressure liquid chromatography using a cation-exchange resin column and wherein arginine is

detected by derivatization and gas chromatography-mass spectrometry or wherein the level of nitric oxide is detected by conversion assay of labeled arginine to labeled citrulline and nitric oxide.

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L5: Entry 41 of 72 File: USPT Jan 5, 1999

DOCUMENT-IDENTIFIER: US 5856158 A
TITLE: Purified nitric oxide synthase from rat brain

Brief Summary Text (5):
Nitric oxide synthases (NOS, EC 1.14.23) are important enzymes, which convert L-arginine to L-citrulline and nitric oxide (NO). Nitric oxide is a very short-lived free radical, which is rapidly oxidized to nitrite (NO.sub.2) and nitrate (NO.sub.3) which are measured as the stable inactive end products of nitric oxide formation. The significance, however, lies in the fact that NO appears to play a pivotal role in a wide variety of physiological and pathological processes in mammals. These processes include vasodilation and regulation of normal vascular tone, inhibition of platelet aggregation, neuronal transmission, cytostasis, hypotension associated with endotoxic shock, inflammatory response-induced tissue injury, mutagenesis, and formation of carcinogenic N-nitrosamines (Nathan, FASEB J. 6:3051-3064 (1992); Kiechle et al., Am. J. Clin. Pathol. 100:567-575 (1993)). For example, it is well-known in the art to treat humans afflicted with angina distress and cardiovascular disease with nitroglycerin, which acts as a vasodilating agent. In the body, nitroglycerin is converted to nitric oxide (NO), which is the pharmacologically active metabolite. See, Palmer et al., Nature 333:664-666 (1988). Thus, evidence that NO mediates functions as diverse as those which occur in the brain, the endothelium and the blood, has led to intense study into the biological roles of NO and the various distinct members of the NOS family. (See, e.g., Marletta, J. Biol. Chem. 268:12231-12234 (1993); Knowles et al., Biochem. J. 298:249-258 (1994)).

Detailed Description Text (61):
The anti-nNOS-II antibody and nNOS-inhibitors are also effective when immobilized on a solid support. Examples of such solid supports include, but are not limited to, plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, and acrylic resins, such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir et al., "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10 (1986), Jacoby et al., Meth. Enzym. 34 Academic Press, N.Y. (1974)).

Other Reference Publication (30):
Kwon et al., "L-citrulline production from L-arginine by macrophage nitric oxide synthase," J. Biol. Chem. 265:13442-13445 (1990).

Other Reference Publication (47):
Pufahl et al., "Mechanistic probes of N-hydroxylation of L-arginine by the inducible nitric oxide synthase from murine macrophages," Biochemistry 31:6822-6828 (1992).

Other Reference Publication (52):
Stuehr et al., "N.sup..omega. -hydroxy-L-arginine is an intermediate in the biosynthesis of nitric oxide from L-arginine," J. Biol. Chem. 266:6259-6263 (1991).

WEST Search History

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DATE: Monday, October 25, 2004

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☐	L5	l4 and immobiliz$	72
☐	L4	arginine adj5 (nitric adj1 oxide)	526
☐	L3	argine adj5 (nitric adj1 oxide)	1
☐	L2	argine adj5 no	0
☐	L1	urokinase adj5 arginine	67

END OF SEARCH HISTORY